

## Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension

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Uncontrolled and controlled clinical trials with different compounds and procedures are reviewed to define the risk-benefit profiles for therapeutic options in pulmonary arterial hypertension (PAH). A grading system for the level of evidence of treatments based on the controlled clinical trials performed with each compound is used to propose an evidence-based treatment algorithm. The algorithm includes drugs approved by regulatory agencies for the treatment of PAH and/or drugs available for other indications. The different treatments have been evaluated mainly in idiopathic PAH, heritable PAH, and in PAH associated with the scleroderma spectrum of diseases or with anorexigen use. Extrapolation of these recommendations to other PAH subgroups should be done with caution. Oral anticoagulation is proposed for most patients; diuretic treatment and supplemental oxygen are indicated in cases of fluid retention and hypoxemia, respectively. High doses of calcium-channel blockers are indicated only in the minority of patients who respond to acute vasoreactivity testing. Nonresponders to acute vasoreactivity testing or responders who remain in World Health Organization (WHO) functional class III, should be considered candidates for treatment with either an oral phosphodiesterase-5 inhibitor or an oral endothelin-receptor antagonist. Continuous intravenous administration of epoprostenol remains the treatment of choice in WHO functional class IV patients. Combination therapy is recommended for patients treated with PAH monotherapy who remain in WHO functional class III. Atrial septostomy and lung transplantation are indicated for refractory patients or where medical treatment is unavailable. (J Am Coll Cardiol 2009;54:S78–84) © 2009 by the American College of Cardiology Foundation

In 1891, Ernst von Romberg, a German physician, described an autopsy subject as having “pulmonary vascular sclerosis”; however, it is only since 1995 with the introduction of intravenous epoprostenol that disease-specific targeted medical therapies for pulmonary arterial hypertension (PAH) have become available. Furthermore, significant advances in the treatment of PAH have occurred during the past 15 years. Currently 9 medical therapies have either received regulatory approval or are under regulatory review. These agents target the prostacyclin pathway, the nitric oxide pathway, and the

endothelin pathway. Combination trials have demonstrated additive or synergistic benefit by targeting 2 or all 3 of these pathways.

Until the 1980s, attempts to reduce pulmonary arterial pressure were performed with nonselective (pulmonary and systemic) vasodilators. Favorable and sustained results were convincingly shown only with the use of high doses of calcium-channel blockers (CCBs) and only in the minority of patients who responded to acute vasoreactivity testing (1–6). In addition, oral anticoagulant treatment was considered effective on the basis of retrospective or uncontrolled studies (1,7–9). In the 1990s, treatment with continuous IV administration of epoprostenol was shown in 3 nonblinded randomized clinical trials (RCTs) to improve symptoms, exercise capacity, and hemodynamic status in PAH and to improve survival in idiopathic pulmonary arterial hypertension (IPAH)/heritable pulmonary arterial hypertension (HPAH) (10–12). During that period, favorable results of several uncontrolled series of PAH patients who underwent atrial septostomy or lung transplantation were also reported (13–16).

Twenty RCTs with 9 new compounds as monotherapy have been completed in PAH patients (10–12,17–31). In addition, 6 RCTs testing combinations of agents (e.g., endothelin-

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receptor antagonists [ERAs] and phosphodiesterase [PDE]-5 inhibitors, or prostanoid and ERA or PDE-5 inhibitors) have been completed (32–37). Approximately 5,000 patients have participated in these studies aimed at developing effective treatments for PAH.

The conclusions derived from clinical trials over the past 15 years have provided us with an evidence-based treatment strategy. The purpose of the present report is to review the RCTs performed in PAH and to propose an evidence-based updated treatment algorithm that incorporates currently available therapies. This algorithm can be used worldwide, subject to the availability of specific drug therapies.

### Uncontrolled Clinical Studies in PAH

**Anticoagulants.** The evidence for favorable effects of oral anticoagulant treatment in patients with IPAH, HPAH, or PAH associated with anorexigens is based on retrospective analyses from 7 studies, of which 5 were positive and 2 were negative (1,7–9). The survival of anticoagulated patients selected on the basis of clinical judgment was improved, as compared with a concurrent population that was not treated with oral anticoagulants. Three-year survival improved from 21% to 49% in the series reported by Fuster et al. (7); and the 3- and 5-year survival rates increased from 31% to 47% and from 31% to 62%, respectively, in the series reported by Rich et al. (1). These studies were not randomized, and one can argue that the lower survival of the control groups could be related to comorbidity that precluded the use of anticoagulation in the untreated patients. In addition, only IPAH, HPAH, and anorexigen-related PAH patients were included in the studies. In recent RCTs, approximately 70% of patients were treated with oral anticoagulants (10–12,17–37). Interestingly, the highest prevalence of oral anticoagulant treatment was seen in the trials involving mainly IPAH and HPAH patients in World Health Organization (WHO) functional class III and IV, whereas the lowest prevalence was observed in a trial of patients with scleroderma. It should be emphasized that there is no evidence of any difference in the efficacy of oral anticoagulant therapy on the basis of functional class severity.

**Diuretics, digoxin, and oxygen.** The symptomatic and clinical benefits of diuretic treatment in right heart failure preclude the need for controlled trials to demonstrate efficacy in PAH. In recent RCTs with new treatments, approximately 50% to 70% of patients were treated with diuretics (38,39). The lack of trials with specific classes of diuretics in PAH and individual variability in responses leave the choice of the type and dose of drug to be used in individual cases to the experience of the physician.

Short-term intravenous (IV) administration of digoxin in IPAH produces a modest increase in cardiac output and a significant reduction in circulating norepinephrine (40); no data are available on the effects of long-term treatment. Accordingly, the use of digitalis in PAH patients is based primarily on the judgment of the physician rather than on scientific evidence of efficacy. Digoxin was administered to

approximately 25% to 50% of patients in recent RCTs in PAH (38).

No consistent data are currently available on the effects of long-term oxygen treatment in PAH. Although improvement in pulmonary hypertension (PH) with low-flow supplemental oxygen has been reported in some PAH patients (41), this has not been confirmed in controlled trials. In a controlled study in patients with Eisenmenger syndrome, nocturnal oxygen therapy had no effect on hematologic variables, quality of life, or survival (42); in contrast, a previous study suggested increased survival (43).

**CCBs.** Favorable clinical and prognostic effects of high doses of oral CCB drugs in acutely vasoreactive patients with IPAH have been shown in single-center, non-randomized, uncontrolled studies (1–6). In these studies, the control group consisted of nonresponders, who might have a poorer prognosis, as compared with acutely vasoreactive individuals (3). Furthermore, the demonstration of a consistent reduction of pulmonary artery pressure by acute pharmacologic testing in vasoreactive patients raises ethical questions concerning the appropriateness of performing placebo-controlled clinical trials in these patients.

A definition of “a positive acute vasoreactive response” to predict long-term response with high-dose oral CCBs was proposed at the 3rd World Symposium on Pulmonary Hypertension in 2003 (5). With this definition—reduction of mean pulmonary arterial pressure  $\geq 10$  mm Hg to reach a mean pulmonary arterial pressure  $\leq 40$  mm Hg with a normalized or increased cardiac output with acute pulmonary vasodilator challenge with either inhaled nitric oxide or intravenous epoprostenol— $<10\%$  of IPAH patients have a positive acute vasoactive response.

Favorable results of long-term administration of high doses of oral CCBs have also been shown in children with IPAH (4,6). In contrast, the effects of high-dose CCBs on associated forms of PAH have not yet been clearly demonstrated (41). Acute vasodilator testing is recommended for all PAH patients, even though patients with IPAH and anorexigen-induced PAH are more likely to respond. Furthermore, although functional class IV patients are less likely to respond than functional class II and III patients, some functional class IV patients might respond favorably to acute vasodilator testing and might benefit from CCBs; however, it is recommended that these patients be evaluated in a specialized PH center. Empirical treatment with CCBs without a positive response

### Abbreviations and Acronyms

<b>CCB</b>	= calcium-channel blocker
<b>ERA</b>	= endothelin receptor antagonist
<b>ET<sub>A</sub></b>	= endothelin receptor A
<b>ET<sub>B</sub></b>	= endothelin receptor B
<b>HPAH</b>	= heritable pulmonary arterial hypertension
<b>INR</b>	= international normalized ratio
<b>IPAH</b>	= idiopathic pulmonary arterial hypertension
<b>IV</b>	= intravenous
<b>PAH</b>	= pulmonary arterial hypertension
<b>PDE</b>	= phosphodiesterase
<b>PH</b>	= pulmonary hypertension
<b>RCT</b>	= randomized controlled trial
<b>WHO</b>	= World Health Organization

with acute vasodilator testing using either inhaled nitric oxide or IV epoprostenol is contraindicated (41).

**Surgical and interventional procedures.** Lung transplantation or atrial septostomy might be indicated in select patients who progress despite optimal medical therapy or for whom medical therapy is not available. Lung transplantation and atrial septostomy are discussed in detail in another article in this supplement (44).

### Controlled Clinical Trials in PAH

**Synthetic prostacyclin and prostacyclin analogues.** The efficacy of continuous IV administration of epoprostenol (synthetic prostacyclin) has been evaluated in 3 unblinded, controlled clinical trials: 2 in IPAH/HPAH (10,11), and 1 in PAH associated with the scleroderma spectrum of diseases (12). Although IV epoprostenol improves symptoms, exercise capacity, and hemodynamic status in both clinical conditions, survival was increased only in IPAH and HPAH.

Five RCTs with 3 prostacyclin analogues as monotherapy have been performed in PAH patients (19,45). The effects of continuous subcutaneous administration of treprostinil were assessed in a pilot RCT in which the improvement in exercise capacity was not statistically significant (45). In the 2 pivotal RCTs, improvements were reported in symptoms, exercise capacity, and hemodynamic status (19). Continuous IV administration of treprostinil seems to be safe and effective on the basis of 2 small, open-label, uncontrolled studies in patients with PAH (46,47).

The orally active prostacyclin analogue beraprost was evaluated in PAH patients in 2 RCTs, 1 in Europe (20) and 1 in the U.S. (23). In the first study, an increase in exercise capacity was seen after 3 months. In the second, which lasted 12 months, improvement in exercise capacity was observed at 3 and 6 months but not thereafter (23). No hemodynamic improvements were observed in the 12-month study, and clinical events were reduced only at the 6-month evaluation.

Inhaled iloprost as monotherapy was evaluated in 1 RCT that enrolled patients with both PAH and chronic thromboembolic PH (21). Overall, this study showed an increase in exercise capacity and improvement in symptoms, pulmonary vascular resistance, and clinical events in PH patients. Continuous IV administration of iloprost was shown to be effective in a small, open-label, uncontrolled series of patients with PAH and chronic thromboembolic PH (48).

**Endothelin receptor antagonists.** Nine RCTs using 1 of 3 ERAs as monotherapy have been performed in PAH patients. The orally active endothelin receptors A and B (ET<sub>A</sub>/ET<sub>B</sub>) ERA bosentan was evaluated in 4 RCTs in PAH patients (17,22,27,30,49), including 1 RCT performed in a cohort of patients with the Eisenmenger syndrome (27) and 1 RCT performed in a cohort of patients with only mildly symptomatic PAH (30). Overall, bosentan improved exercise capacity, functional class, hemodynamic status, echocardiographic and Doppler variables, and time to clinical worsening (17,22,27,31,49). Small increases in the dose of warfarin might

be required to maintain therapeutic international normalized ratio (INR) when bosentan is coadministered with warfarin.

Sitaxsentan, an orally active ET<sub>A</sub> selective ERA, has been assessed in PAH patients in 2 RCTs, both of which demonstrated improvement in exercise capacity (assessed by the 6-min walk test) and hemodynamic status (25,28,50). In 1 of the 2 studies (25), the primary end point (peak oxygen consumption as assessed by cardiopulmonary exercise testing) was not statistically significant. Coadministration of sitaxsentan and warfarin requires the reduction of the warfarin dose up to 80% to maintain a therapeutic INR, due to a drug-drug interaction.

Ambrisentan, an orally active ET<sub>A</sub> selective ERA, has been evaluated in 3 RCTs (29,51,52). Results showed improvements in exercise capacity and clinical events that seem similar to the results observed with the other 2 ERAs.

On the basis of the results of RCTs using ERAs, the incidence of elevated hepatic transaminases  $\geq 3$  times the upper limit of normal seems to be approximately 10% with bosentan, approximately 4% with sitaxsentan, and approximately 2% with ambrisentan. The patient populations in the various RCTs differed, and these numbers should be considered only as approximations and may not be comparable.

**PDE-5 inhibitors.** Two RCTs with 2 different PDE-5 inhibitors have been performed in PAH patients (26,31). Used as monotherapy, both sildenafil and tadalafil improved exercise capacity and hemodynamic status in approximately 50% of enrolled patients; tadalafil also improved clinical events (31).

The optimal agent for PAH monotherapy remains unclear.

**Combination therapy.** More recently, combination treatment has been evaluated to address the multiple pathobiologic mechanisms present in PAH. The combination of oral bosentan and IV epoprostenol was investigated in 1 small study, with inconclusive results (32). Five additional RCTs have evaluated combination therapy in PAH. The addition of inhaled iloprost to background oral bosentan demonstrated improved hemodynamic status and clinical events in 1 RCT (35); however, these results were not confirmed in an open trial (34). In another study, the addition of oral sildenafil to background IV epoprostenol demonstrated improved exercise capacity, hemodynamic status, and clinical events; furthermore, in post hoc analysis, the addition of oral sildenafil to background IV epoprostenol increased survival versus IV epoprostenol alone (37). In the pivotal tadalafil RCT, approximately 50% of the patients had oral tadalafil added to background oral bosentan; in that study overall, tadalafil improved exercise capacity, hemodynamic status, and clinical events (31). Inhaled treprostinil has also been studied as add-on therapy to either background bosentan or background sildenafil; in both combinations, the addition of inhaled treprostinil improved exercise capacity (36). These studies support the efficacy of combination treatment in patients who remain symptomatic on monotherapy. The optimal combination on the basis of overall risk-benefit considerations remains unknown.

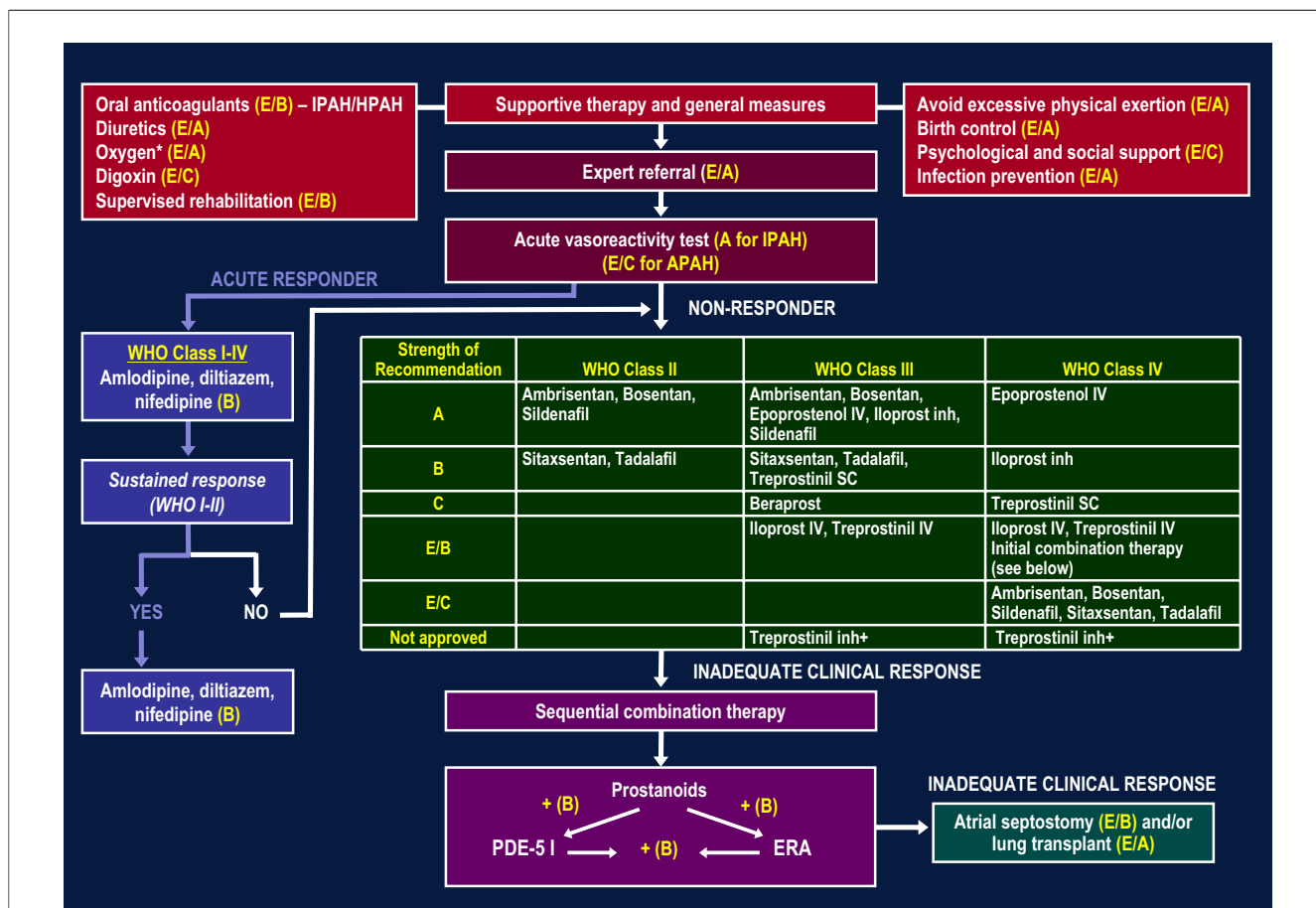
Although there seems to be an interaction between sildenafil and bosentan (increased bosentan and decreased sildenafil

levels) (53), the clinical relevance of this is unclear. Similarly, although the interaction between tadalafil and bosentan is less than that between sildenafil and bosentan (i.e., tadalafil exposure decreased with minimal changes in bosentan exposure) (54), the clinical relevance is also unknown. Tadalafil has also been evaluated in the presence of ambrisentan, with no clinically relevant pharmacokinetic interactions reported (55). There is no clinically relevant pharmacokinetic interaction between ambrisentan and sildenafil (56), with no dose adjustment of ambrisentan or sildenafil recommended compared with administration of either drug alone. There is a minimal interaction reported between sitaxsentan and sildenafil, with no changes in sitaxsentan plasma concentrations in the presence of sildenafil and only modest increases in sildenafil plasma concentrations (57). Overall, no dose adjustments have been recommended for patients treated with 1 of the aforementioned ERAs in combination with either sildenafil or tadalafil.

**Early intervention.** For functional class II or III patients, the role of early aggressive intervention (i.e., IV epoprostenol as first-line treatment), either as monotherapy or in conjunction with either a PDE-5 inhibitor and/or an ERA, remains

unknown. Although the first RCTs in PAH focused primarily on functional class III and IV patients, results from a more recent RCT evaluating the efficacy of bosentan in only mildly symptomatic PAH patients support early intervention (30). In addition, prespecified subgroup analyses of the sildenafil, tadalafil, and ambrisentan RCTs did not show any significant differences in the therapeutic efficacy of these drugs between patients in WHO functional classes II and III (30). The apparent lack of “catch-up” in placebo-treated patients supports early intervention in PAH (41). Future studies seem warranted.

**General comments on controlled clinical trials.** Although these studies have similar designs, treatment duration, and end points, analyses of baseline WHO functional class and etiology profiles show substantial differences. Accordingly, comparisons might be misleading. Improvement of exercise capacity as assessed by the 6-min walk test has been observed in all of these studies, albeit to different degrees. In evaluating the clinical relevance of exercise capacity improvements, additional elements, such as baseline functional class, effects on combined clinical events (e.g., hospital stays, mortality, rescue therapies),



**Figure 1 PAH Evidence-Based Treatment Algorithm**

Drugs within the same grade of evidence are listed in alphabetical order and not order of preference. Not all agents listed are approved or available for use in all countries. Strengths of recommendations are defined in Table 1. \*To maintain oxygen at 92%. +Investigational, under regulatory review. APAH = associated pulmonary arterial hypertension; ERA = endothelin receptor antagonist; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; SC = subcutaneous; WHO = World Health Organization.

**Table 1** Quality of Evidence, Net Benefit, and Strength of Recommendation

Variables	Description
<b>Quality of the evidence</b>	
Good	Evidence is based on good randomized controlled trials or meta-analyses.
Fair	Evidence is based on other controlled trials or randomized controlled trials with minor flaws.
Low	Evidence is based on nonrandomized, case-control, or other observational studies.
Expert opinion	Evidence is based on the consensus of the carefully selected panel of experts in the topic field. There are no studies that meet the criteria for inclusion in the published reports review.
<b>Net benefit</b>	
Substantial	
Intermediate	
Small/weak	
None	
Conflicting	
Negative	
<b>Strength of recommendation</b>	
A	Strong recommendation
B	Moderate recommendation
C	Weak recommendation
D	Negative recommendation
I	No recommendation possible (inconclusive)
E/A	Strong recommendation on the basis of expert opinion only
E/B	Moderate recommendation on the basis of expert opinion only
E/C	Weak recommendation on the basis of expert opinion only
E/D	Negative recommendation on the basis of expert opinion only

and hemodynamic effects, should be considered. As mentioned previously, a survival benefit has been demonstrated in only 1 controlled, third-party-blinded study of IV epoprostenol in patients with severe IPAH/HPAH (11). Because, on the basis of these results, IV epoprostenol is considered rescue therapy, subsequent RCTs assessing mortality as an end point could not ethically be performed. Furthermore, severely ill subjects requiring IV epoprostenol treatment were excluded in recent RCTs, resulting in a low mortality in these study populations. A recent meta-analysis performed on all RCTs in PAH patients published through October 2008 reports a 43% decrease in mortality and a 61% reduction in hospital stays in patients treated with targeted therapies versus patients randomized to placebo (39). These results, achieved after an

average treatment period of 14.3 weeks, support the efficacy of the currently approved PAH treatments.

**Evidence-Based Treatment Algorithm**

A treatment algorithm based on a consensus of the PH community evaluating the clinical trials presented in this review is presented in Figure 1. The recommendations in this guideline are based on a grading system in which the strength of the recommendation results from the interaction of 2 components: the quality of the evidence, and the net benefit of the therapy (Tables 1 and 2). Because treatments have been evaluated primarily in IPAH, HPAH, and PAH associated with scleroderma or anorexigen use, extrapolation of these recommendations to other PAH subgroups should be done with caution.

**Conclusions**

The suggested initial approach after the diagnosis of PAH is to treat patients with oral anticoagulant drugs if no contraindication exists, diuretics in cases of fluid retention, and supplemental oxygen in cases of hypoxemia, even though RCTs with these compounds are lacking. Patients should be referred without delay to centers experienced in acute vasoreactivity testing and the treatment of pulmonary vascular diseases. Acute vasoreactivity testing should be performed in all patients with PAH, although patients with IPAH, HPAH, and PAH associated with anorexigen use are the most likely to exhibit a positive response. Vasoreactive patients, as defined in the preceding text, should be treated with optimally tolerated doses of CCBs; maintenance of response, defined as WHO functional class I or II with near-normal hemodynamic status, should be confirmed by repeat right heart catheterization and clinical assessment after 3 to 6 months of treatment. Nonresponders to acute vasoreactivity testing or responders who remain in WHO functional class III should be considered candidates for treatment with either a PDE-5 inhibitor or an ERA. Among prostanoids, treprostinil is administered subcutaneously, intravenously, or by inhalation; iloprost can be given intravenously or by inhalation; beraprost is administered orally, and epoprostenol is administered intravenously.

The choice of drug is dependent on a variety of factors, including the approval status, route of administration, side-effect profile, patient preference, and the physician's experience and clinical judgment. Continuous IV epoprostenol remains first-line therapy for PAH patients in WHO functional class IV, because of its demonstrated survival benefit in IPAH/

**Table 2** Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits

Quality of Evidence	Net Benefit					
	Substantial	Intermediate	Small/Weak	None	Conflicting	Negative
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	I	I	D
Expert opinion	E/A	E/B	E/C	I	I	E/D

See Table 1 for definition of designations.

HPAH, with extrapolation to associated PAH patients in WHO functional class IV. Combination therapy should be considered for patients who fail to show improvement or who deteriorate with monotherapy. The goal in treating PAH patients is to improve WHO functional class III and IV patients to functional class I or II and to improve all functional class II patients to functional class I or at least to maintain functional class II in patients presenting in that functional class. Finally, both atrial septostomy and lung transplantation are indicated in carefully selected patients for refractory PAH or in cases where medical treatments are unavailable. These procedures should be performed only in experienced centers.

Major therapeutic advances for PAH patients have been achieved in the last decade; however, none of the currently approved therapies represents a cure for this progressive disease. The search for such treatments continues, with promising new concepts arising from a better understanding of the pathobiology of pulmonary vascular diseases. Patients and physicians should be encouraged to foster such research by participating in RCTs conducted at specialized PH centers.

#### Author Disclosures

Dr. Barst has received honoraria for serving as a consultant, advisory board member, and/or speaker from Actelion, Eli Lilly, GlaxoSmithKline, Gilead, Novartis, and Pfizer. Dr. Gibbs has received honoraria for advisory boards and/or lecturing from Actelion, Bayer Schering, GlaxoSmithKline, Pfizer, and United Therapeutics, and has been an investigator in trials sponsored by BioMarin and Lung Rx. Dr. Ghofrani has received honoraria and research funds from Actelion, Bayer Schering, Encysive, ErgoNex Pharma, GlaxoSmithKline, Novartis, and Pfizer. Dr. Hoepfer has received pharmaceutical grants from Actelion, Bayer Schering, and Encysive; travel accommodations and speaker's honoraria from Actelion, Encysive, GlaxoSmithKline, Lung Rx, Pfizer, and Schering; and has served as a consultant to Actelion, Bayer Schering, Encysive, GlaxoSmithKline, and Lung Rx. Dr. McLaughlin has received honoraria and/or consulting fees from Actelion, Gilead, MondoBIOTECH, and United Therapeutics. The University of Michigan has received research grants from Actelion, Pfizer, and United Therapeutics. Dr. Rubin has received research grants from Actelion, Gilead, the National Heart, Lung and Blood Institute, Pfizer, and United Therapeutics; and has served on advisory committees for Actelion, Gilead, and Pfizer; and served as a consultant for Actelion, Aires Pharmaceuticals, Bayer Schering Pharma, Cerulean Biosciences, Gilead, mondoBIOTECH, the National Heart, Lung and Blood Institute, Onyx Pharmaceuticals, Pfizer, Solvay Pharmaceuticals, and United Therapeutics. He owns stock in United Therapeutics. Dr. Sitbon has received fees for lectures from Actelion, Bayer Schering, GlaxoSmithKline, Pfizer, and United Therapeutics; is a member of advisory boards for Actelion, GlaxoSmithKline, and Pfizer; and has received research grants from Actelion, Bayer Schering, GlaxoSmithKline, and Pfizer. Dr. Tapson has received research grants from Actelion, Gilead, GlaxoSmithKline,

Pfizer, and United Therapeutics; and has served as a consultant and on advisory boards for Actelion, Gilead, and United Therapeutics. Dr. Galiè has served on advisory boards for Actelion, Eli Lilly, Encysive, Gilead (Myogen), GlaxoSmithKline, mondoBIOTECH, Pfizer, and Schering; and has received lecture fees from Actelion and Schering. His Institute has received grant support from Actelion, Eli Lilly, Encysive, Gilead (Myogen), MondoBIOTECH, Pfizer, Schering, and United Therapeutics.

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**Key Words:** algorithm ■ evidence-based treatment ■ pulmonary arterial hypertension.







# Managing chronic thromboembolic pulmonary hypertension: pharmacological treatment options

I.M. Lang

**ABSTRACT:** Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition in which organised thrombi obstruct the pulmonary vessels, causing increased pulmonary vascular resistance, progressive pulmonary hypertension (PH) and right heart failure. The treatment of choice is pulmonary endarterectomy, which restores pulmonary haemodynamics with acceptable periprocedural mortality rates in the majority of suitable patients. However, CTEPH may be inoperable owing to surgically inaccessible thrombi or comorbid diseases that confer an unacceptably high risk.

Pharmacotherapies, although not yet approved, may be useful in this situation or for treating residual or recurrent PH following surgery. Vasodilator drugs for PH are attracting growing interest as potential treatments for CTEPH because this disease has recently been labelled as a “dual” pulmonary vascular disorder: major vessel obstruction and remodelling is combined with a small vessel arteriopathy that is histologically indistinguishable from the classical pulmonary arteriopathy observed in pulmonary arterial hypertension.

Of three completed randomised controlled trials in patients with CTEPH, only one was powered to detect a treatment effect. The BENEFIT trial employed the dual endothelin-receptor antagonist bosentan. Although haemodynamics improved significantly, the second component of the primary end-point, exercise capacity, was not met.

More evidence is required to resolve whether vasodilator treatments are beneficial for inoperable chronic thromboembolic pulmonary hypertension.

**KEYWORDS:** Chronic thromboembolic pulmonary hypertension, drug therapy, review

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition in which organised thrombi obstruct the pulmonary vessels, causing increased pulmonary vascular resistance, progressive pulmonary hypertension (PH) and right heart failure. CTEPH is associated with considerable morbidity and mortality [1], and forms group IV of the current World Health Organization (WHO) classification system for PH [2]. However, there are many uncertainties surrounding CTEPH as the incidence and prevalence of this disease are not well characterised, aspects of CTEPH pathogenesis are poorly understood, diagnostic approaches have not been standardised, and this field lacks randomised, controlled trials and guidelines [1]. An international, prospective, observational registry was set up in 2007 to resolve these uncertainties, and data has now been collected from >600 patients with CTEPH. Recruitment is progressing rapidly, and the first presentation of results is expected in 2009 [3]. Currently, estimates of CTEPH incidence

range from 0.1–0.5% of patients surviving an acute pulmonary embolism (PE) [4, 5], to a cumulative incidence following an acute PE of 0.8% after ~4 yrs [6], or 3.8% after 2 yrs in another study [7]. However, CTEPH may be more common than these results suggest as the majority of CTEPH cases never experience acute PE [8].

CTEPH is a potentially correctable cause of PH, and vascular disobliteration by pulmonary endarterectomy (PEA) is the treatment of choice [9]. In-hospital mortality rates for patients who have undergone PEA range from 5% to 24% [5, 10, 11], and in general, periprocedural mortality rates of 5–11% are achieved [1, 9, 12]. However, not all patients are eligible for surgery because of an inaccessible and/or distal thromboembolism, or serious comorbidities [13, 14]. Moreover, PH can persist or reappear in patients who have undergone PEA, and persistent PH is one of the most important determinants of post-PEA outcome [11, 15, 16]. Furthermore, high mean pulmonary

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arterial pressure ( $P_{pa}$ ) is an independent predictor of death in patients with “chronic PE” ( $p=0.04$ ) [17]. Taken together, these factors reveal a need for effective therapy for CTEPH.

The present article will focus on recent developments in the pharmacological treatment of CTEPH. Current thoughts regarding the epidemiology, risk factors, prognosis and vascular biology of this disease will also be considered.

### **PATHOGENESIS, RISK FACTORS AND VASCULAR BIOLOGY**

Our understanding of CTEPH has developed in recent years such that it is now viewed as a complex “dual” vascular disorder. This has been demonstrated by investigations into the relationship between pulmonary vascular obstruction and haemodynamic status in patients with acute PE and those with CTEPH [18]. Whereas increases in mean  $P_{pa}$  and total pulmonary resistance correlated with the degree of pulmonary vascular obstruction in patients with PE [18], no such correlation was detectable for patients with CTEPH. This suggests that PH in CTEPH is not solely because of obstruction of proximal pulmonary arteries, but is also due to the remodelling of small distal arteries in non-occluded areas.

The majority of experts now agree that there is compelling evidence supporting the concept that PE, either overt or occult, triggers a cascade of events that eventually result in CTEPH [1, 5]. Persistent obstruction of pulmonary arteries may result in elevated  $P_{pa}$  and high shear stress in areas of the pulmonary vasculature that were spared from thromboembolic occlusion. Thus, acute PE is likely to be the initiating event, but progression of PH results from misguided pulmonary vascular remodelling (*i.e.* major and small vessel disease) [1, 19]. This theory is also supported by the histopathology of resistance vessels in the pulmonary vascular bed, which show arteriopathic changes not only in areas directly affected by the PE, but also in portions that were not involved (fig. 1) [1, 20]. Despite evidence linking CTEPH to PE, an alternative pathogenic



**FIGURE 1.** Material removed by pulmonary endarterectomy from the right and left pulmonary artery. The specimen is an example of type III disease (fibrosis, intimal webbing and thickening within distal segmental arteries, with no visible thrombus) [9].

hypothesis has been suggested in which pulmonary vascular occlusions are caused by a primary arteriopathy of pulmonary vessels and secondary *in situ* thrombosis [21]. Supporters of this theory point out that there is a lack of documented history of previous deep vein thrombosis or PE in ~50% of CTEPH cases, although it should be remembered that asymptomatic venous thromboembolism is very common [22, 23].

The embolic and alternative hypotheses of CTEPH pathogenesis may be unified if the factors that influence the incomplete resolution of PE and organisation of thrombi in these patients are considered. These hypotheses have been elucidated in experiments by LANG *et al.* [24], which showed that no abnormalities were detected in the expression of fibrinolytic proteins or in responses to thrombin stimulation in primary endothelial cells cultured from pulmonary arteries of patients with CTEPH. However, elevated expression levels of endothelial plasminogen activator inhibitor and factor VIII have been shown in organised thromboemboli of CTEPH [25]. This suggests that *in situ* thrombosis within vascularised, fibromuscular obstructions may contribute to the persistence of pulmonary (and also peripheral) venous thrombi in CTEPH [13]. In addition to *in situ* thrombosis, other factors that might influence the incomplete resolution of PE and organisation of thrombi in patients with CTEPH include infection [19], inflammation and autoimmunity [26]. It should be noted that recent research suggests that infection with Staphylococci in patients with CTEPH enhances fibrotic vascular remodelling after thrombosis, resulting in misguided thrombus resolution, thus thrombus infection appears to be a trigger in the evolution of CTEPH [19].

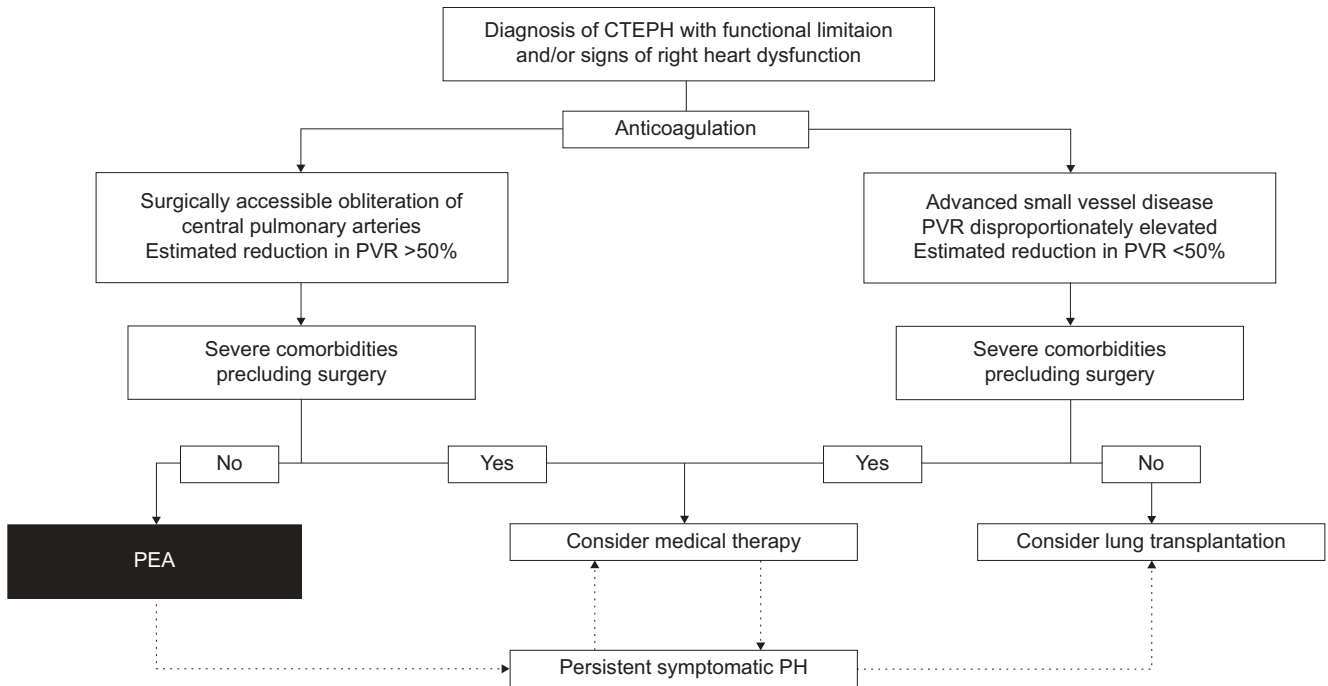
Clinical risk factors have been investigated by BONDERMAN *et al.* [26]. This case-control study compared 109 patients with CTEPH to those with confirmed acute non-fatal PE ( $n=187$ ). An increased risk of CTEPH was associated with prior splenectomy (odds ratio (OR) 13, 95% confidence interval (CI) 2.7–127), ventriculo-atrial shunt for the treatment of hydrocephalus (OR 13, 95% CI 2.5–129) and chronic inflammatory disorders, such as osteomyelitis and Crohn’s disease (OR 67, 95% CI 7.9–8,832). A further study also identified splenectomy as a risk factor for CTEPH [27], and a recent retrospective cohort study involving 687 patients with CTEPH showed that thyroid replacement therapy (OR 6.10, 95% CI 2.73–15.05) and a history of malignancy (OR 3.76, 95% CI 1.47–10.43) were novel risk factors for CTEPH [28].

### **THERAPEUTIC OPTIONS FOR CTEPH**

#### **Current conventional treatments**

The decision of how to treat each patient is complex and requires a multidisciplinary team of cardiologists, pulmonologists, radiologists and surgeons to estimate the degree of haemodynamic improvement that might be expected after surgery [1, 12]. These decisions are still based on the clinical experience of the multidisciplinary team, but the current therapeutic algorithm is useful in guiding this process (fig. 2) [1]. Essentially, all patients with CTEPH receive lifelong anticoagulant medication to prevent recurrent thromboembolic events, and ideally a 3-month period of watchful waiting should elapse before a full diagnostic workup and any decision regarding choice of treatment [1].

The primary treatment for suitable cases of CTEPH is PEA. PEA is performed under hypothermia and total circulatory



**FIGURE 2.** Algorithm for the therapeutic approach for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Where practical, pulmonary endarterectomy (PEA) is the preferred approach. Medical therapy refers to prostanoids, endothelin-receptor antagonists or phosphodiesterase-5 inhibitors, although there is currently a lack of firm evidence to support the use of these drugs. PVR: pulmonary vascular resistance; PH: pulmonary hypertension. Dashed arrows symbolise therapeutic considerations in case the initial approach fails. Modified from [1] with permission from the publisher.

arrest, and involves the removal of obstructive material from each pulmonary artery, and its lobar and segmental branches (20–30 branches in total; fig. 1) [12]. As has been previously mentioned, PEA is associated with excellent results: when performed in experienced centres and on carefully selected patients, PEA is associated with low periprocedural mortality rates (e.g. 5–11%) and generally results in near normalisation of haemodynamics and substantial improvements in clinical symptoms [1, 9, 12].

Although there is no doubt that all patients who are suitable for PEA should receive this surgical intervention [9], there is less certainty surrounding the use of other treatment options. These are usually limited to pharmacotherapies, although lung transplantation can be successful in certain cases with perioperative mortality rates of ~20% for patients with PH or CTEPH [12]. Nonspecific supportive therapies are also used in the management of post-PE patients, but these do not generally affect the underlying CTEPH disease processes [29]. In addition to the aforementioned anticoagulation, these include diuretics to treat fluid overload and oxygen to correct hypoxaemia. Calcium channel blockers have rarely been an option for treating CTEPH because true haemodynamic responders are rare and are almost exclusively observed among operable patients [29, 30].

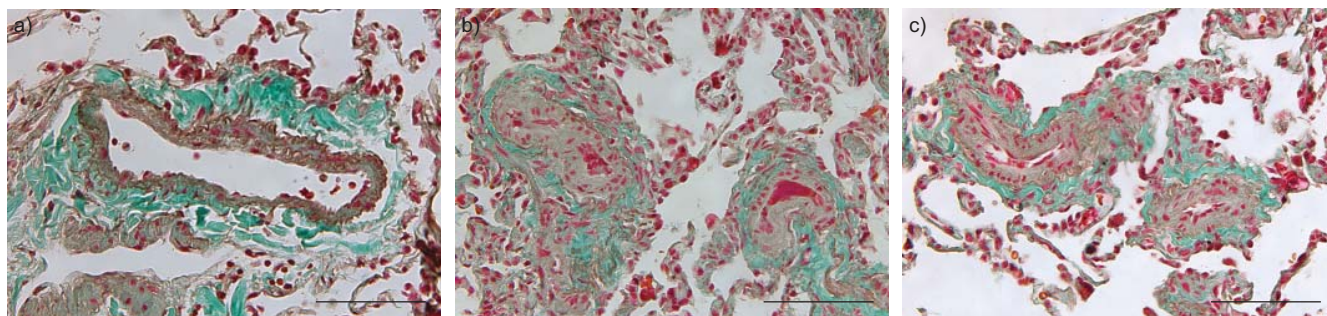
**Pharmacotherapies**

CTEPH has recently become regarded as a dual pulmonary vascular disorder in which major vessel obstruction and remodelling combine with a small vessel arteriopathy, which is histologically indistinguishable from the classical pulmonary

arteriopathy observed in PAH (fig. 3b). This has been demonstrated by a histopathological study of small pulmonary artery tissue from 31 patients with an established diagnosis of CTEPH, which found pulmonary hypertensive lesions (fig. 3c), including plexogenic lesions [20]. It has been proposed that such lesions most likely represent the nonspecific effect of chronic PH on exposed (non-occluded) areas of the vasculature [31]. Therefore, it is reasonable to assume that medical therapies for PH, targeting the three main pathways involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary artery in patients with PH (i.e. the endothelin, prostacyclin or nitric oxide pathways) [32], may be effective for patients with CTEPH. Such treatments may be particularly useful in the following situations: 1) where there is inoperable distal disease or comorbidities that make PEA a high-risk option; 2) as a therapeutic bridge to PEA or lung transplant for high-risk patients; or 3) for patients with persistent or residual PH after PEA [29].

Although a number of small pilot studies and uncontrolled trials have targeted all three clinical scenarios, the remainder of this article will focus on the few randomised, controlled trials of PH drugs for patients with CTEPH who are unable to undergo PEA.

The three randomised, controlled trials in patients with CTEPH performed to date have used a prostanoid (iloprost) [33], a phosphodiesterase-5 inhibitor (sildenafil) [34] and an endothelin-receptor antagonist (bosentan) [35]. Iloprost, 2.5 or 5.0 µg, inhaled six to nine times daily (median dose 30 µg·day<sup>-1</sup>) for 12 weeks, was compared with placebo for a



**FIGURE 3.** Histological sections of small pulmonary arterioles from a) normal lungs, and b) lungs of patients with pulmonary arterial hypertension and c) chronic thromboembolic pulmonary hypertension, demonstrating medial hypertrophy and intimal fibrosis with near occlusion. Scale bar=100  $\mu$ m.

population of 203 patients that included 57 patients with inoperable CTEPH at baseline [33]. Because of this mixed population, it is difficult to draw any firm conclusions concerning the treatment of CTEPH. However, results were analysed according to type of PH (labelled as primary *versus* nonprimary), and these data showed that patients with nonprimary PH and primary PH experienced similar improvements in Mahler dyspnoea score and health-related quality of life in response to treatment with iloprost. A double-blind, placebo-controlled, 12-week pilot study has investigated the use of sildenafil, 40 mg three times daily, in 19 patients with inoperable CTEPH [34]. Unfortunately, this study was inadequately powered to test the primary end-point (change in 6-min walk distance). Moreover, there was no significant difference between the sildenafil and placebo groups (17.5 m improvement). Nevertheless, there were significant improvements in WHO functional class ( $p=0.025$ ) and pulmonary vascular resistance ( $p=0.044$ ) for the sildenafil-treated group.

A larger randomised controlled study of pharmacotherapy has been carried out in 157 patients with anatomically inoperable CTEPH who are unable to undergo PEA: the BENEFIT (bosentan effects in inoperable forms of chronic thromboembolic pulmonary hypertension) study was completed recently [36]. Studies examining the pathophysiology of CTEPH in humans and animal models have provided the following rationales for the use of endothelin-receptor antagonists in CTEPH: 1) endothelin is a potent endogenous vasoconstrictor [37]; 2) endothelin signalling pathway components are upregulated in CTEPH [38]; and 3) endothelin-mediated pulmonary vascular remodelling has been demonstrated in a canine model of CTEPH [39]. Bosentan, administered for 16 weeks, reduced pulmonary vascular resistance by 24% compared with placebo ( $p<0.0001$ ), although there was no significant benefit in terms of 6-min walking distance [35, 36]. Larger, longer-term studies are required to evaluate a potential effect of pharmacotherapy on exercise capacity.

### CONCLUSIONS

The results from clinical trials of CTEPH pharmacotherapies are far from conclusive, and there is not yet an approved drug for this indication. Nevertheless, there is clearly a need for pharmacotherapies in clinical practice. It is interesting to note that survival rates for patients given medical treatments, with or without surgery, appear to have improved in recent years. This was revealed by a study of 469 patients with CTEPH, of

whom 148 (32%) had distal, nonsurgically treated disease [39]. Survival rates from time of diagnosis to 1 or 3 yrs later were 82% and 70% for the nonsurgical group and 88% and 76% in surgically treated patients, respectively. Most of the nonsurgical patients received disease-modifying pharmacotherapies; until 2004 these treatments were mainly prostanoids, but from 2004 onwards most were either an endothelin-receptor antagonist or phosphodiesterase-5 inhibitor. The same study also showed changing trends regarding the increased use of these disease-modifying pharmacotherapies before PEA. Before 2004, 29% of patients received these drugs before PEA but from 2004 onwards this rate was 65% [40].

In summary, there is an urgent need for further clinical trials of pharmacotherapies for chronic thromboembolic pulmonary hypertension to resolve the role of these treatments in a constantly growing population of off-label treated patients.

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